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CORRESPONDENCE

Why we should not recommend or offer fluvoxamine to COVID-19 patients?

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To the Editor,

The answer to the posted question is rather straightforward: not only there is no explicit evidence of a benefit of fluvoxamine in COVID-19 patients, but there is rather explicit evidence of no (relevant) benefit. The apparently reasonable pharmacodynamic/pharmacokinetic rationale [1, 2] and a huge amount of observational data (too extensive to be individually addressed here)–although commonly contradictory–have indicated a possibility that early commenced fluvoxamine in COVID-19 outpatients might prevent disease progression; or that fluvoxamine in hospitalized and even critical (e.g., managed in intensive care units, ICU) COVID-19 patients might reduce mortality. Regarding the former (mildly symptomatic COVID-19 outpatients, fluvoxamine within 7 days since diagnosis), randomized placebo-controlled trials (RCT) are rather consistent in showing no relevant benefit: (i) initially, a small STOP-COVID 1 RCT [3] (fluvoxamine 2 × 100 to 3 × 100 mg/day, 15 days $n = 80$, placebo $n = 72$) indicated a reduced 15-day hospitalization/new onset hypoxemia rate, but only 6 events were recorded (0/80 vs. 6/72); (ii) the trial extension, STOP-COVID 2 (never published) [4], however, found no benefit: 11/272 (4.0%) events vs. 12/275 (4.4%); (iii) the TOGHETHER trial [5] (fluvoxamine 2 × 100 mg/day, 10 days, $n = 741$, placebo $n = 756$) indicated a mild reduction in 28-day hospitalization rates (10.0% vs. 13.0%); (iv) a small South Korean trial (fluvoxamine 2 × 100 mg/day, 10 days, $n = 26$, placebo $n = 26$; outcomes as in STOP-COVID) found no indication of a treatment benefit (2 events vs. 2 events) [6]; (v) the recent COVID-OUT RCT [7] (fluvoxamine 2 × 50 mg/day, 14 days, $n = 334$, placebo $n = 327$) found similar 14-day rates of a composite of new onset hypoxemia, hospitalization, emergency room visit or death (24.0% vs. 24.9%) and of each of its components; (vi) finally, the recent ACTIV-6 trial [8] (fluvoxamine 2 × 50 mg/day, 10 days, $n = 674$, placebo $n = 614$) reported similar 28-day hospitalization/emergency room visit rates (3.9% fluvoxamine vs. 3.8% placebo) and similar time to recovery (HR = 0.96, 95%CrI 0.86–1.07). Recommending or offering a non-functional treatment is unethical, and "publicizing" its existence might generate a false sense of security in those reluctant to receive vaccination if being viewed as a helpful alternative resource.

Why, then, do many colleagues support (in this or that way) the use of fluvoxamine in this setting? To this question, the answer is a more complex one. Undoubtedly driven by good intentions and facing an unprecedented pandemic of a devastating disease, we might have developed a cognitive bias and are prone to see what we would like to see, rather than the objective "state of the matter," particularly when resources are limited. However, a large part of the problem is elsewhere [9, 10]: (i) much of the published medical research is methodologically inadequate and misleading; (ii) much of

it is both carried out and published for wrong reasons (the latter might be particularly applicable to COVID-19-related manuscripts [11]); (iii) most healthcare professionals are not aware of this problem and lack the skills needed to evaluate reliability and usefulness of data. This is particularly so with non-randomized/observational data which tend to be perceived and interpreted as if coming from valid experiments although commonly burdened by a range of biases unrecognized by the readers, and seemingly also by journal editors (see, e.g., [12] as a worked-out critique of a published study advocating fluvoxamine benefits, which was so heavily flawed that it should best be completely ignored; see [13] for the elaboration of biases particularly common in observational studies on COVID-19).

If the tendency of publishing research on fluvoxamine in COVID-19 that is of highly questionable validity continues, we might find ourselves in a situation that is almost impossible to rectify—we would not be able to discourage the public in their views of fluvoxamine as a "wonder drug," just as we are unable to rectify the confusion about ivermectin.]

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Declarations

Competing interests The author declares no competing interests.

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